

Remarks

Courtesies extended to Applicant's representative during the telephone interview held on February 21, 2007, are acknowledged with appreciation.

As discussed during the telephone interview, the present invention provides methods for improving the likelihood of success in achieving crystallographic structure determination employing hydrogen exchange analysis. The method includes the use of hydrogen exchange analysis to identify unstructured regions of a protein, which are then deleted to obtain one or more modified proteins for crystallization and structure determination.

Claims 1-48 were pending before this communication. By the present communication, claims 1, 42 and 43 have been amended to define Applicant's invention with greater particularity. The amendments add no new matter as they are fully supported by the original specification and claims. Claims 1-48 remain pending with claims 18-19 and 44-48 withdrawn from consideration (the non-elected claims are retained herein pending final disposition of the elected claims). The present status of all claims in the application is provided in the Listing of Claims presented herein beginning on page 2.

In addition, in conjunction with the submission of a Sequence Listing herein, by the present communication, paragraphs [0052] – [0054], [0057], [0059] – [0063] and [0065] have been amended to insert SEQ ID NO identifiers associated with each listed sequence.

Compliance with Sequence Rules

The observation that several figures of the application contain sequences without any SEQ ID NOs is noted. Submitted herewith is a Sequence Listing, computer readable form thereof, and a statement in accordance with 37 C.F.R. § 1.821(f). No new matter has been added because all of the sequences included in the Sequence Listing were present in the application as originally filed.

Claim objections

The observation that claims 6 and 12 contain non-elected subject matter is acknowledged. However, amendment of these claims is deferred pending resolution of the elected claims, in view of the possible rejoinder of non-elected subject matter.

Claim rejection under 35 USC § 112, second paragraph

The rejection of claims 1-17 and 20-43 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite, is respectfully traversed. Specifically with respect to the phrase “unstructured region” of a protein, Applicant respectfully submits that the term is described throughout the specification. See e.g., paragraphs [0068], [0073] and [0074]. See also, paragraph [0084] at page 25 of the specification:

As used herein, unstructured regions of a protein are those where contiguous stretches of primary sequence exhibit fast exchange rates, indicative of complete and continuous solvation of the amide hydrogens in such segments. Further, as used herein, very unstructured regions refer to linear stretches of primary sequence in which the rates of exchange of each amide hydrogen in the segment is very fast, typically greater than about 90% of amide hydrogens are saturation-deuterated in about 10 seconds or less at 0 °C. These very unstructured regions are then targeted for deletion in accordance with the methods of the present invention.

Thus, contrary to the Examiner’s assertion, the specification clearly describes the term “unstructured region.”

Applicant respectfully disagrees with the Examiner’s assertion that claims 1-17 and 20-42 are allegedly “indefinite because the use of a ‘wherein’ clause does not constitute an active method step” (Office Action, page 6, lines 3-4). Applicant respectfully submits that one of ordinary skill in the art would readily understand that the step within the wherein clause would

constitute a precondition which must be satisfied before the required “subjecting to crystallization and structure determination one or more modified forms(s) of said protein” can be carried out. However, in order to reduce the issues and expedite prosecution, the claims have been amended to specifically recite the steps of “identifying” and “deleting” in addition to “subjecting.” Applicant submits that this rejection has been rendered moot.

Claim rejections under 35 U.S.C. § 112, first paragraph--enablement

The rejection of claims 1-17 and 20-43 under 35 U.S.C. § 112, first paragraph as allegedly lacking enablement (see pages 6-9 of the Office Action), is respectfully traversed. Specifically, Applicant respectfully disagree with the Examiner’s assertion that the specification allegedly “does not reasonably provide enablement for crystallographic structure determination of a protein by possibly crystallizing a protein that has had its highly flexible region removed wherein the highly flexible region was identified by hydrogen exchange analysis.” (Office Action, page 6, lines 19-22). Each of the steps of identifying, deleting and subjecting can be readily carried out as provided by the specification. However, in order to be reduce the issues and expedite prosecution, the preamble of claim 1 now recites “improving the chances of” which is consistent with the Examiner’s suggestions (Office Action, p. 9, lines 11-13). As such, Applicant respectfully submits that this rejection has been rendered moot.

The rejection of claims 1-17 and 20-43 under 35 U.S.C. § 112, first paragraph as allegedly lacking enablement (see pages 9-12 of the Office Action), is respectfully traversed. Specifically, Applicant respectfully disagrees with the Examiner’s assertion that the specification allegedly “does not reasonably provide enablement for identifying said highly flexible region using any or all methods of hydrogen exchange analysis.” (Office Action, page 9, lines 20-22).

The Examiner acknowledges that the specification is enabling for “a method of improving the chances a protein will crystallize . . . using deuterium hydrogen exchange mass spectrometry analysis.” (Office Action, p. 9, lines 15-17). The use of deuterium hydrogen exchange mass spectrometry is provided as an exemplary hydrogen exchange method for use in

the practice of the present invention. The use of this exemplary method demonstrates that the claimed method does in fact improve the likelihood of protein crystallization. Moreover, the use of other hydrogen exchange methods are also contemplated, e.g., the use of tritium is also described throughout the specification, for example, at paragraphs [0012]-[0022] (entitled "Tritium Exchange Techniques"), [0021] and [0226]-[0230].

Furthermore, the claims do not require "unambiguous resolution" as alleged by the Examiner. (Office Action, p. 11, line 21). The specification provides methods for improving the likelihood of success of achieving protein crystallization, which the Examiner has acknowledged is enabled. (Office Action, p. 9, lines 11-19). Hydrogen exchange mass spectrometry is but one of the steps of the claimed method; information from any method of hydrogen exchange allows one to carry out the claimed method. As such, Applicant respectfully submits that the claims are enabled and Applicant requests reconsideration and withdrawal of the rejection.

Claim rejections under 35 USC § 102(b)

The rejection of claims 1-17 and 20-42 under 35 U.S.C. § 102(b) as allegedly being anticipated by Dale et al. (Acta Cryst. 1999, D55, 1626-1629), is respectfully traversed.

In order to anticipate a claim, a single prior art reference must provide each and every element set forth in the claim. Furthermore, the claims must be interpreted in light of the teaching of the specification. *In re Bond*, 15 USPQ2d 1566, 1567 (Fed. Cir. 1990). *See also* MPEP § 2131.

The present invention, as exemplified by claim 1, provides a method of improving the likelihood of success of achieving crystallographic structure determination by identifying unstructured regions using hydrogen exchange analysis, deleting at least one unstructured region identified by hydrogen exchange analysis and subjecting the protein to crystallization.

Dale fails to disclose the use of hydrogen exchange analysis, as is required by the instant claims as exemplified in independent claim 1. As such, Dale fails to disclose each and every

limitation of the claims. Applicant respectfully requests reconsideration and withdrawal of the rejection.

Double Patenting

The provisional rejection of claims 1-43 on the ground of nonstatutory obviousness-type double patenting as allegedly being unpatentable over claims 1-43 of copending Application No. 10,997,436, is respectfully traversed.

Contrary to the Examiner's assertion, the instant claims and copending application 10/997,436 are not obvious variants of one another. The claims of application 10/997,436 require at least two hydrogen exchange analyses whereas the instant claims encompass a single hydrogen exchange analysis. For at least this reason, reconsideration and withdrawal of this objection are respectfully requested.

Conclusion

In view of the above amendments and remarks, reconsideration and favorable action on all claims are respectfully requested. In the event any matters remain to be resolved in view of this communication, the Examiner is encouraged to call the undersigned so that a prompt disposition of this application can be achieved.

Respectfully submitted,

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